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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Serial No. 10/677,734

Customer No. 23379

Applicant: Gardner et al.

Confirmation No. 4912

Filed: Oct 01, 2003

Group Art Unit: 1652

Docket No. UTSD:1510-1

Examiner: Swope, Sheridan

Title: *Foreign PAS Ligands Regulate PAS Domain Function*

CERTIFICATE OF TRANSMISSION
I hereby certify that this corr is being transmitted by facsimile to the Comm for Patents 571-273-8300 on March 17, 2007.
Signed _____
Richard Aron Osman

AMENDED BRIEF ON APPEAL

The Honorable Board of Appeals and Interferences
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Honorable Board:

Responsive to the Notice dated Mar 13, 2007, this Amended Brief is identical to that filed Jan 10, 2007 except for expressly stating that claims 1-20 are canceled. We appeal from the Examiner's Jan 05, 2007 final rejection of claim 21.

REAL PARTY IN INTEREST

The real party in interest is the Board of Regents, the University of Texas System, the assignee of this application.

RELATED APPEALS AND INTERFERENCES

An appeal is pending in related application 10/677,733; Appellants are unaware of any other related appeals or interferences.

PAGE 1/20 * RCVD AT 3/17/2007 12:47:26 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/19 * DNIS:2738300 * CSID:9492181767 * DURATION (mm-ss):42-10

cfc received 20 pages.

STATUS OF CLAIMS

Claim 21 is rejected and subject to this appeal; claim 22 is withdrawn as directed to a nonelected group. Claims 1-20 are canceled.

STATUS OF AMENDMENTS

All Amendments are believed to be properly before the Board.

SUMMARY OF CLAIMED SUBJECT MATTER

A method of changing a functional surface binding specificity of a selected PAS (Per-ARNT-Sim) domain, wherein the PAS domain is folded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity, the method comprising the steps of: (a) introducing into the hydrophobic core of the PAS domain a foreign ligand of the PAS domain; and (b) detecting a resultant change in the functional surface binding specificity of the PAS domain (Specification, p.3, lines 3-8; claim 21); in particular, wherein the PAS domain is HIF2a PAS B (Specification, p.3, line 18; claim 21), and the binding specificity is an intramolecular binding affinity of the PAS domain (Specification, p.3, lines 9-10; claim 21), detected as a change in chemical shifts detected by 1H/15N-HSQC NMR (Specification, p.13, line 29; claim 21).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. WHETHER THE EXAMINER HAS PROPERLY REJECTED CLAIM 21 UNDER 35USC112, FIRST PARAGRAPH (Enablement).

II. WHETHER THE EXAMINER HAS PROPERLY REJECTED CLAIM 21 UNDER 35USC112, FIRST PARAGRAPH (Written Description).

III. WHETHER THE EXAMINER HAS PROPERLY REJECTED CLAIM 21 UNDER 35USC103(a).

ARGUMENT

I. THE EXAMINER HAS NOT PROPERLY REJECTED CLAIM 21 UNDER 35USC112, FIRST PARAGRAPH (Enablement).

The claim is directed to a method of changing a functional surface binding specificity of a selected PAS domain by (a) introducing into the hydrophobic core of the PAS domain a foreign ligand of the PAS domain; and (b) detecting a resultant change in the functional surface binding specificity of the PAS domain, wherein ...the binding specificity is an intramolecular binding affinity of the PAS domain, detected as a change in chemical shifts detected by 1H/15N-HSQC NMR.

As explained in the Specification, suitable foreign ligands may be screened from libraries of synthetic or natural compounds, and conventional SAR analyses provide ligands of higher affinity and/or specificity (Specification, p.6, lines 9-10). This process was specifically exemplified with HIF2a PAS B, wherein a library of 772 compounds (Specification p.13, lines 6-14) was screened for HIF2a PAS B binding using 1H/15N-HSQC NMR; as seen in Figure 1, 21 hits were obtained for HIF2a PAS B (see also, Specification, p.18, line 1). From these the inventors developed a "lead" HIF2a PAS B ligand (Specification, top of p.31).

The Specification confirms that the foreign ligands bind the hydrophobic core of HIF-2 PAS B, and as a result, alter the functional surface binding specificity of the PAS domain, wherein the binding specificity is an intramolecular binding affinity of the PAS domain detected as a change in chemical shifts detected by 1H/15N-HSQC NMR:

> Our structural studies confirm that core ligand binding in each HIF-2 PAS B and ARNT PAS B induces distal changes in PAS domain structure, and functional binding studies confirm resultant changes in DNA:HIF-2 :ARNT transcription complex formation and DNA binding specificity (e.g. Michel et al., Biochim Biophys Acta. 2002 Oct 11;1578(1-3):73-83). Table 3 show exemplary identified foreign ligands of HIF-2a PAS B and ANRT PAS B, respectively, which specifically bind within their hydrophobic cores and disrupt complex formation. Specification, p.18, lines 21-26.

The practitioner does not require any a priori structural characteristics of the recited "foreign ligand" to practice the method. As demonstrated, the method is typically practiced using a library of compounds which need not be structurally characterized.

As for the cited step of introducing into the foreign ligand into the hydrophobic core of the PAS domain, this can be effected by simply mixing a PAS domain-containing protein with the ligand in solution (Specification, p.20, lines 7-8).

As demonstrated by the Specification (supra) and the uncontroverted evidence of record (Expert Declaration under 37CFR1.132, attached below), one skilled in the art would have been readily able to practice this without undue experimentation.

II. THE EXAMINER HAS NOT PROPERLY REJECTED CLAIM 21 UNDER 35USC112, FIRST PARAGRAPH (Written Description).

The claim is directed to a method of changing a functional surface binding specificity of a selected PAS domain by (a) introducing into the hydrophobic core of the PAS domain a foreign ligand of the PAS domain; and (b) detecting a resultant change in the functional surface binding specificity of the PAS domain, wherein the PAS domain is HIF2a PAS B....

As explained in the Specification, suitable foreign ligands may be screened from libraries of synthetic or natural compounds, and conventional SAR analyses provide ligands of higher affinity and/or specificity (Specification, p.6, lines 9-10). This process was specifically exemplified with HIF2a PAS B, wherein a library of 772 compounds (Specification p.13, lines 6-14) was screened for HIF2a PAS B binding using 1H/15N-HSQC NMR; as seen in Figure 1, 21 hits were obtained for HIF2a PAS B (see also, Specification, p.18, line 1). From these the inventors developed a "lead" HIF2a PAS B ligand (Specification, top of p.31).

The Specification confirms that the foreign ligands bind the hydrophobic core of HIF-2 PAS B, and as a result, alter the functional surface binding specificity of the PAS domain, wherein the binding specificity is an intramolecular binding affinity of the PAS domain detected as a change in chemical shifts detected by 1H/15N-HSQC NMR:

> Our structural studies confirm that core ligand binding in each HIF-2 PAS

B and ARNT PAS B induces distal changes in PAS domain structure, and functional binding studies confirm resultant changes in DNA:HIF-2 :ARNT transcription complex formation and DNA binding specificity (e.g. Michel et al., Biochim Biophys Acta. 2002 Oct 11;1578(1-3):73-83). Table 3 show exemplary identified foreign ligands of HIF-2a PAS B and ANRT PAS B, respectively, which specifically bind within their hydrophobic cores and disrupt complex formation. Specification, p.18, lines 21-26.

The practitioner does not require any a priori structural characteristics of the recited "foreign ligand" to practice the method. As demonstrated, the method is typically practiced using a library of compounds which need not be structurally characterized.

As demonstrated by the Specification (supra) and the uncontroverted evidence of record (Expert Declaration under 37CFR1.132, attached below), the Specification amply describes and exemplifies the claimed methods to one skilled in the art.

III. THE EXAMINER HAS NOT PROPERLY REJECTED CLAIM 21 UNDER 35USC103(a) OVER Vogtherr (EXS. 2003, 93, 183-202) OR Amezcua (Structure 2002, 10, 1349-61) IN VIEW OF Ema (PNAS USA, 1997, 94, 4273-8) IN FURTHER VIEW OF Fukunaga (J Biol Chem 1995, 270, 29270-8).

The claim is directed to a method of changing a functional surface binding specificity of a selected PAS domain, wherein the PAS domain is folded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity by (a) introducing into the hydrophobic core of the PAS domain a foreign ligand of the PAS domain; and (b) detecting a resultant change in the functional surface binding specificity of the PAS domain, wherein the PAS domain is HIF2a PAS B, and the binding specificity is an intramolecular binding affinity of the PAS domain detected as a change in chemical shifts detected by 1H/15N-HSQC NMR.

Vogtherr (2003) generally describes the use of NMR-based screening for lead discovery; Amezcua (2002) describes the used of NMR to detect ligand binding to PAS kinase; Ema (1997) reports that *HIF1a* heterodimerizes with Arnt (note that HIF1a is structurally and functionally

distinct from the recited HIF2a; Sowter (Cancer Res, 2003, 63, 6130-34); and Fukunaga (1995) reports identification of functional domains of the aryl hydrocarbon receptor.

Prior to the present disclosure, HIF was known to be regulated in several ways by oxygen availability, but only via mechanisms that are based on oxygen-sensitive enzymes that covalently modify portions of the HIFa subunit at sites distant to the PAS domains (Expert Declaration under 37CFR1.132, attached below, and citations therein). These prior findings taught away from any expectation that the HIF PAS domains would be sensory. In addition, HIF2a PASB presents a well-folded domain lacking the dynamic regions of PASK PAS A (Amezucua et al., 2002, p.1352, col.1, lines 10-12) and long insertion loops of NPAS2 PAS A (Erbel et al., 2003, PNAS 100, 15504-9), further removing any expectation of core ligand binding. Furthermore, we have of record uncontroverted evidence in the form of an expert Declaration, confirming that one skilled in the art at the time of our filing would not have expected HIF2a PAS to provide a core for sensory ligand binding.

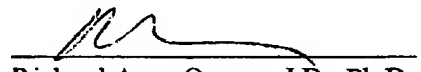
The Action correctly states that the inventors' prior publication (Amezucua et al., 2002) disclosed that hPASK PAS A has a well-packed hydrophobic core, yet was able to bind small organic molecules, and speculated that other PAS domains, including those that do not copurify with ligands when isolated from natural sources, may serve sensor roles in vivo. However, as noted above, hPASK PAS A also demonstrated "unusual flexibility ... near the ligand binding sites" (Amezucua et al., 2002, p.1352, col.1, lines 10-12). This unusual flexibility near the ligand binding site is what led the authors to hypothesize that hPASK PAS A might be able to bind small organic molecules despite its NMR-apparent well-packed core (id.) -- and this unusual flexibility near the ligand binding site is not present in HIF2a PASB. Also as noted above, unlike the situation with hPASK, HIF was previously known to be regulated by non-PAS mechanisms. It is because of their structural and functional distinctions, that there is no suggestion anywhere that HIF2a PAS would or could provide a receptor for small organic molecules, and no one skilled in the art would try to impose on HIF2a PASB an inference drawn from a functionally and structurally distinct protein like HPASK PAS A. And the foregoing is documented in the uncontroverted expert declaration of record.

Though the cited art does not support a prima facie case for obviousness, for good

measure we have of record uncontroverted affirmative evidence documenting the fact that one skilled in the art would have considered the claimed invention nonobvious at the time it was made (Expert Declaration under 37CFR1.132, attached below).

Appellants respectfully request reversal of the pending Final Action by the Board of Appeals. The appeal brief fee was provided Jan 10, 2007 by an accompanying PTO-2038.

Respectfully submitted,
SCIENCE & TECHNOLOGY LAW GROUP



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CLAIMS APPENDIX

1-20 (cancelled)

21. A method of changing a functional surface binding specificity of a selected PAS domain, wherein the PAS domain is folded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity, the method comprising the steps of:

introducing into the hydrophobic core of the PAS domain a foreign ligand of the PAS domain; and

detecting a resultant change in the functional surface binding specificity of the PAS domain,

wherein the PAS domain is HIF2a PAS B, and the binding specificity is an intramolecular binding affinity of the PAS domain, detected as a change in chemical shifts detected by 1H/15N-HSQC NMR, wherein PAS refers to Per-ARNT-Sim, ARNT refers to acyl hydrocarbon receptor nuclear translocator, and HIF2a refers to hypoxia inducible factor 2 alpha.

22. (pending/withdrawn) A method of changing a functional surface binding specificity of a selected PAS domain, wherein the PAS domain is folded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity, the method comprising the steps of:

introducing into the hydrophobic core of the PAS domain a foreign ligand of the PAS domain; and

detecting a resultant change in the functional surface binding specificity of the PAS domain,

wherein the PAS domain is HIF2a PAS B and is present as part of HIF2a, and the binding specificity is an intermolecular binding affinity of the PAS domain detected as a change in transcription complex formation of DNA: the HIF-2a: ARNT.

RELATED PROCEEDINGS APPENDIX

No decisions in any related proceedings are known to exist.

EVIDENCE APPENDIX

The following relied-upon evidence of record is appended below:

1. 132 Declaration of Professor Stephen R. Sprang dated Jun 19, 2006; provided with our Response dated Jun 22, 2006; entered and considered by the Action dated Sep 01, 2006.

2. Sowter (Cancer Res, 2003, 63, 6130-34); provided with our Response dated Jun 22, 2006; entered and considered by the Action dated Sep 01, 2006.

3. Erbel et al., 2003, PNAS 100, 15504-9; provided with our Response dated Jun 22, 2006; entered and considered by the Action dated Sep 01, 2006.